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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/774,325	FINKE ET AL.
	Examiner	Art Unit
	Christine Foster	1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _26 June 2007_.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final..

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _1-3,5,9,11-13 and 15-20_ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1-3,5,9,11-13 and 15-20_ is/are rejected.

7)☒ Claim(s) _9, 15, and 18_ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _21 February 2006_ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment, filed 6/26/07, is acknowledged and has been entered. Claims 1, 9, 13, 15-16, 18, and 20 were amended. Claims 1-3, 5, 9, 11-13, and 15-20 are currently pending and under examination.

2. It is noted that the amendment presents claim 19 with the status identifier "Currently Amended", which appears to be incorrect because no changes are indicated through the use of markings in the claim and no changes appear to have been made relative to the prior version of the claim. See MPEP 714.

Objections/Rejections Withdrawn

3. The objection to the specification as containing new matter is withdrawn in response to Applicant's amendments to remove the incorporation by reference statement (see Reply, pages 2 and 6).

4. The objection to claim 13 for failing to further limit has been withdrawn in response to Applicant's formulation of the claim in independent form.

5. The objection to claim 15 has been obviated by the amendments.

6. The rejections of claim 15 under 35 USC 112, 1st paragraph (new matter) as set forth in the previous Office action have been withdrawn in response to Applicant's amendments to remove the terminology "in the absence of a crosslinking agent" and to recite that the protein size is as "determined by photon correlation spectroscopy".

7. The rejection of claim 16 under 35 USC 112, 1st paragraph (new matter) as set forth in the previous Office action (page 13, item 30) is withdrawn in response to the amendments to remove the term "about".

8. The rejections under 112, 2nd paragraph have been obviated by the amendments.

Claim Objections

9. Claims 9, 15, and 18 are objected to because of the following informalities:

10. Claims 9 and 18 recite "the microparticles…consists", which should apparently read --the microparticles…consist--.

11. Claim 15 refers to "polystyrene microparticles" in the plural in the preamble and in steps (a) and (e) but to "the polystyrene microparticle" in the singular in step (c). It is suggested that step (c) also refer to microparticles in the plural.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-3, 5, 9, 11-13, and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

14. Claim 15 (as amended in the instant Reply of 6/26/07) now recites that the combination is incubated "in the absence of covalent coupling" (see step (d) of the claim).

Applicant's Reply indicates that the amendment is supported at [0003]-[0005] and at [0022], to which the Examiner disagrees for the following reasons.

It is clear from the specification at [0003]-[0005] that Applicant's invention involves attachment of proteins to polystyrene microparticles by *adsorption* rather than by *covalent coupling*. Thus, adequate support is found for attachment of proteins to polystyrene microparticles by adsorption, as distinguished from by covalent coupling. However, the disclosure of "covalent coupling" only pertains to the nature of attachment of protein to microparticle. This meaning was already conveyed in step (c) of claim 15, which refers to "adsorbing" the protein onto the microparticle.

See also Applicant's Reply at page 9, the first full paragraph, which refers to "covalent coupling *to bind proteins to microparticles*" (emphasis added).

The instant limitation is not commensurate with the scope of this teaching. Rather, the currently claimed limitation requires more generally that the proteins are incubated with polystyrene microparticles "in the absence of covalent coupling". This would exclude not only covalent coupling in regards to the attachment between proteins and microparticles (which is adequately described in the specification), but would also rule out any type covalent bond formation occurring among any of the components of the combination. For example, the limitation would rule out intramolecular covalent bond formation in the context of an adsorbed protein molecule or covalent bond formation among different adsorbed protein molecules.

In particular, it is noted that the limitation is apparently being used to distinguish over the Schmid reference, in which proteins are first adsorbed (non-covalently) to microparticles and then subjected to UV light irradiation. As argued by Applicant, UV light irradiation is known to result in covalent bond formation (Reply, page 15), such that the UV irradiation step performed by Schmid would apparently have the effect of cross-linking the adsorbed proteins to each other.

However, cross-linking of the proteins *to each other* after they have been adsorbed (non-covalently) to the microparticles is distinct from covalent vs. noncovalent attachment of the proteins to the microparticles.

The disclosure of attachment of proteins to microparticles by adsorption vs. by covalent coupling does not adequately support the currently claimed step, which requires that the proteins are incubated together with the microparticles for 1-10 days in the absence of any type covalent bond formation.

The stipulation that the adsorbed protein-polystyrene microparticle combination be incubated "in the absence of covalent coupling" therefore represents a negative limitation that is not fully supported by the original disclosure. MPEP 2173.05(i) states:

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983), aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

In the instant case, the specification only includes a positive recitation wherein the

attachment of proteins to microparticles may be performed by "covalent coupling". However, the claims exclude covalent coupling not only with respect to the linkage between proteins and microparticles, but in general, which would also completely exclude covalent coupling with respect to any intermolecular or intramolecular covalent reactions involving the adsorbed proteins. Because the element of "covalent coupling" is only positively disclosed in the specification in reference to the nature of the interaction between proteins and microparticles, its explicit exclusion generically in the claims lacks adequate basis in the original disclosure and therefore represents new matter.

15. The amendments to claims 1 and 15 in the Reply of 2/23/07 introduce new matter in that claim 1 now recites that the coating step is conducted "at a pH **selected from a range of about 10.5 to about 12.5**". Similarly, claim 15 now recites that the pH is "**selected from the range of about 10.5 to about 12.5**".

The amendments of 2/23/07 to insert the term "**about**" in relation to the claimed pH ranges broadens the scope of the claims in a manner unsupported by the original disclosure.

Applicant's reply states that new matter has not been introduced (see the Reply, page 5), but did not specifically indicate where support for the amendments may be found. The examiner was unable to find support in the specification and claims as originally filed for the claimed methods involving pH values of "**about** 10.5 to **about** 12.5".

Although the specification discloses that coating is preferably carried out at a pH range of "**10.5 to 12.5**" (see [0030]), there is no written description of the claimed range of "**about 10.5 to about 12.5**".

The insertion of the term "**about**" broadens the scope of the claims so as to include pH values of, for example, pH 13.5, which are not described in the specification. Such broadening amendments, in going beyond the scope of the original disclosure, depart from the specification and claims as originally filed.

16. Claims 13 and 17 (as introduced by Applicant's amendment of 2/23/07) present new matter because they recite that the coating step is conducted with a buffer "having a salt content of **about** 0.3 to **about** 1.5 M". The specification discloses at [0031] that:

> The coating is preferably carried out with a buffer which has a salt content of 0.1 to 2 M, particularly preferably 0.3 to 1.5 M and especially preferably of 0.8 to 1.2 M.

The specification does not fully support the claimed subject matter because the range "**about 0.3 to about 1.5 M**" is broader in scope than the disclosure of "**0.3 to 1.5 M**".

17. Claims 9 and 18 present new matter because they recite that "the microparticles have a size of about 2.8 μm and consists of **about** 88% polystyrene and **about** 12% magnetite". See Applicant's amendment of 2/23/07 and the instant amendments of 6/26/07. The specification discloses at [0022] that:

> DYNABEADS from the DYNAL Company having a size of ca 2.8 μm and consisting of 88% polystyrene and 12% magnetite such as the hydrophobic beads M-280 or the epoxy beads M-270 are, for example, suitable.

The claims represent new matter because the claimed "**about** 88%" polystyrene and "**about** 12%" magnetite is broader in scope that the disclosed values of "88%" and "12%", since the insertion of the term "about" broadens the scope of the claim to include, for example, particles having 87% or 89% polystyrene.

Additionally, the passage above discloses the claimed size and composition only in describing the properties of "**DYNABEADS**". This description of DYNABEADS having the recited size and composition does not fully support the claim, which now encompasses **all microparticles** with a size of about 2.8 μm that consist of **about** 88% polystyrene and **about** 12% magnetite.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Kakabakos et al. ("Immobilization of Immunoglobulins onto Surface-Treated and Untreated Polystyrene Beads for Radioimmunoassays" *Clin. Chem.* 36 (1990), 492-496) in light of Song et al. ("Effects of Cosolvents and pH on Protein Adsorption on Polystyrene Latex: A Dynamic Light Scattering Study" *Journal of Colloid and Interface Science* 221 (2000), 25-37).

Kakobakos et al. teach a method for producing protein-coated polystyrene microparticles (beads), in which a suspension of uncoated polystyrene microparticles (in water) is added to a protein (IgG) to form a combination of pH 9.6. See in particular the abstract and p. 492, left column; p. 492, right column, the first paragraph; and p. 493, left column, the sections "Polystyrene beads and surface treatment" and "Solid-phase immobilization protocol"; and Figures 1 and 3. It is noted that antibodies are specifically mentioned as examples of bioaffinity

binding pairs in the specification at [0025]. As such, the IgG antibody taught by Kakabakos et al. meets the limitation of being a partner of a bioaffinity binding pair.

In the absence of a specific definition or other indication in the specification as to what pH values would be considered to be "about" 10.5-12.5, the pH of 9.6 taught by Kakabakos et al. would be considered to anticipate the claimed pH of "about" 10.5 to 12.5 since it may reasonably be considered "about" 10.5, being within 1 pH unit. In particular, given that the specification exemplifies pH ranges of pH 9-12.5 and 10-12.5 ([0014]-[0016], [0030], [0045], and Figure 1) and does not provide evidence of criticality between pH 9.6 and 10.5, it is reasonable to conclude based on the specification that pH 9.6 would fall within the claim scope.

The IgG is incubated with the microparticles for 24-48 hours in the absence of covalent coupling since coating of the microparticles is by adsorption, which is the same method disclosed in the instant specification (see especially the abstract; p. 493, left column, "Solid-phase immobilization protocol"; the paragraph bridging pages 493-494; and Figure 2). The reference further teaches separating non-adsorbed protein from protein-coated microparticles by washing (p. 493, left column, "Solid-phase immobilization protocol").

Kakobakos et al. do not mention that the IgG has a size from 10 nm to 300 nm.

Song et al. is relied upon as an evidentiary reference to show that IgG meets the claimed size limitation. Song et al. measured the size of this protein by photon correlation spectroscopy ("dynamic light scattering"), which is the same method disclosed in the instant specification [0025]. The reference provides evidence that IgG has a size within the range of 10-300 nm, since for all measurements performed, the hydrodynamic diameter of IgG was within this claimed range (see page 27, "DLS experiments"; Table 3; and page 30 in particular).

Therefore, in light of the evidence of Song et al., the protein of Kakobakos et al. meets the limitation of being a protein of size 10-300 nm.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 16-17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kakabakos et al. (in light of Song) in view of Amiral et al.

Kakabakos et al. is as discussed above under 35 USC 102, which teaches methods substantially as claimed involving incubation times of 1-2 days (24-48 hours). However, the reference fails to specifically teach incubation times of 4-7, or about 4-7, days as in claims 16 and 20. The reference also fails to specifically teach a buffer having a salt content of about 0.3 to about 1.5 M as in claim 17.

In the instant case, the prior art recognized incubation time as a result-effective variable in the adsorption of proteins onto microparticles, including polystytrene microparticles. For example, Amiral et al. (discussed above) teach that the duration of the reaction is one experimental condition that can be adjusted in order to ensure the stability, reactivity, and preservation of the product (column 9, lines 5-50). This is also taught in Kakabakos et al., in that the immobilization of IgG onto the polystyrene beads increased as a function of time (see Figure 2 and the paragraph bridging pages 493-494).

Absent a showing that the particular claimed range of 4-7 days is critical, it would have been obvious to one of ordinary skill in the art to optimize the length of the incubation out of the normal desire of artisans to improve upon what is already known. In particular, it would have been obvious to increase the incubation time in order to achieve increased adsorption of protein onto the beads, given that increasing incubation time was known to have the effect of increasing the amount of protein immobilized. See MPEP § 716.02 - § 716.02(g) for a discussion of criticality and unexpected results.

With respect to claim 17, ionic strength is also recognized in the prior art as a result-effective variable in the process of protein adsorption to solid surfaces, including polystyrene particles.

For example, Amiral et al. teaches that ionic strength is one experimental condition that is adjusted according to the nature of the product to be assayed when adsorbing proteins onto latex particles, in order to ensure the stability, reactivity, and preservation of the product. In particular, the reference teaches that increasing the ionic strength stabilizes adsorbed immunological reagents (column 9, lines 30-50). The reference exemplifies buffers of ionic strength 0.01-0.5M, which overlaps the claimed range of 0.3-1.5M (column 10, lines 4-21).

Absent a showing that the particular claimed range of 0.3 to 1.5M is critical, it would have been obvious to one of ordinary skill in the art to optimize the ionic strength out of the normal desire of artisans to improve upon what is already known, given that it was known in the prior art to conduct adsorption reactions at ionic strengths overlapping the claimed ranges.

In particular, it would have been obvious to increase the ionic strength in order to increase the stability of the adsorbed protein, as taught by Amiral et al.

22. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kakabakos et al. (in light of Song) in view of Amiral et al. as applied to claim 17 above, and further in view of Bangs ("New developments in particle-based immunoassays: introduction" (1996) *Pure & Appl. Chem.* **10**:1873-1879) and Gudiband et al. (US 5,686,244).

Kakabakos et al. and Amiral et al. are as discussed above. Kakabakos et al. teaches polystyrene microparticles, but fails to specifically teach that the particles have a size of about 2.8 microns and consist essentially of about 88% polystyrene and 12% magnetite.

Bangs et al. teach superparamagnetic particles, which can be used in radioimmunoassay, ELISA's, and other assays in order to help pull things out of solution more quickly (page 1876). In particular, magnetic particles allow for fast and easy separation of solid and liquid phases.

Gudiband et al. teach the superparamagnetic DYNAL M-280 Dynabeads, which have a 2.8 micron diameter (column 21, Example VII). These are the same beads disclosed in the instant application as consisting of 88% polystyrene and 12% magnetite [0022]; thus, the beads meet the recited limitations as to the composition. Thus, superparamagnetic particles of the recited size and composition were known in the prior art.

Therefore, it would have been obvious to conduct the method of Kakabakos et al. and Amiral et al. using the M280 microparticles taught by Gudiband et al., rather than the polystyrene beads taught by Kakabakos et al. One would be motivated to use the microparticles of Gudiband et al. because they are superparamagnetic, which permits fast and easy separation of the solid and liquid phase in radioimmunoassays (as taught by Bangs); which is the intended use of the coated particles of Kakabakos et al. (see the title).

It would have been obvious to select the known M280 particles based on its art-recognized suitability for its intended use, in that Gudiband et al. teaches that the particles are superparamagnetic. See MPEP 2144.07. One would have a reasonable expectation of success because Gudiband et al. teach that the particles are capable of being coated with protein for use in specific binding assays.

23. Claim 15-17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kakabakos et al. (in light of Song) in view of Vaynberg et al., Amiral et al., and Lou et al. The references are of record.

Kakabakos et al. and Song are as discussed in detail above under 35 USC 102 (see above for detailed analysis of the reference teachings).

It is noted that claim 15 is currently rejected under both 35 USC 102 and 35 USC 103. As noted above, because the specification does not specifically define or otherwise indicate what pH values would be encompassed by the range of "about 10.5 to about 12.5", it is reasonable to broadly interpret pH 9.6 (as in Kakabakos et al.) as falling within the claimed range.

However, even if pH 9.6 may be subsequently established not to be "about" pH 10.5, the claimed invention is nonetheless found obvious despite this difference, for the following reasons.

It was known in the art at the time of the invention that pH is a result-effective variable in the adsorption of proteins are coated onto particles, as taught by Vaynberg et al., Amiral et al., and Lou et al. It was also known in the prior art to coat proteins onto polystyrene particles at pH values that overlap or fall within the currently claimed pH range.

For example, Amiral et al. teach that when adsorbing proteins onto latex particles (including polystyrene latex), experimental conditions including pH are adjusted according to the nature of the product to be assaying in order to ensure stability, maximum reactivity, reproducibility, and preservation (see especially column 9, lines 30-50; and column 7, lines 1-11 and 49-66). The reference notes in particular that increasing the pH results in *stabilization* of

immunological reagents to be coated, and teaches adsorption at pH in the range of 4-10 (column 9, lines 50-61).

Vaynberg et al. teach that the properties of proteins adsorbed onto polystyrene microparticles can vary in response to pH (p. 467, left column, the second paragraph; p. 470-471, "Adosrption Isotherms"). In particular, increasing pH was found to be associated with a swelling of the hydrodynamic layer thickness, reflecting underlying changes in the structure of the adsorbed protein layer (Figure 8, p. 470, right column, and p. 471, left column, the first full paragraph). Vaynberg et al. exemplify coating protein onto polystyrene microparticles at high pH values including pH 10 (see p. 469, left column; and Figures 2, 6, and 8 in particular; experiments were conducted over the range pH 5.7-10). The reference also teaches that measurements of the layer thickness and layer hydrodynamic radius (which were found to change as a function of pH) can be used to validate models of the adsorbed protein layer structure (page 472).

Lou et al. also teach that adsorption of proteins onto polystyrene particles is affected by pH, temperature, and other factors (column 4, lines 19-33). In particular, the reference teaches that pH can affect the stability of adsorbed proteins, and report that by adsorbing the protein streptolysin-O at high pH values of 8.5-11.9, the resulting product was more stable and the adsorbed protein substantially retained pre-adsorption characteristics (column 3, lines 34-38; column 4, lines 19-63; column 8, lines 53-59).

Therefore, it would have been obvious to one of ordinary skill in the art to conduct the method of Kakabakos et al. at a pH within the recited range of 10.5-12.5 (rather than at pH 9.6) in the course of routine optimization, out of the normal desire of artisans to improve upon what is

already known. In particular, it would have been obvious to optimize the pH and in particular to select pH values within the recited pH ranges, given that it was known in the art to coat proteins onto polystyrene microparticles at pH values up to and in excess of pH 10, as taught variously by Vaynberg et al, Amiral et al., and Lou et al. As such, it would have been obvious to optimize within the ranges taught in the prior art, which overlap the currently claimed ranges. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. MPEP 2144.05.

It would have been obvious to do this since pH is recognized in the prior art as a result-effective variable in methods of adsorbing protein onto polystyrene particles, in that the pH of the coating reaction can affect the structure, stability, reactivity, reproducibility, and preservation, as taught by Amiral et al. Vaynberg et al., and Lou et al.

The Amiral et al. reference provides additional motivation for adsorbing at higher pH, teaching that increasing pH results in stabilization of the coated reagent. Lou et al. also teach that the stability of streptolysin-O protein-coated particles is increased at high alkaline pH (see especially column 4, lines 34-37). As such, it would have been obvious to conduct the method of Kakabakos et al. at higher pH in order to increase the stability of the coated protein.

Vaynberg et al. teach that the structure of the adsorbed protein can change as a function of pH, and that measurements of the adsorbed protein layer can be used to generate structural models (see especially pages 470-471, “Adsorption Isotherms”; and p. 472). As such, it would have been obvious to increase the adsorption pH in order to generate structural models to study the structure of the protein as a function of pH.

Moreover, Vaynberg et al. teaches that adsorption of protein onto polystyrene is dominated by hydrophobic interactions, such that there is "little variation" in the level of adsorption over a broad range of pH values, including alkaline pH values of up to pH 10 (see the entire document, especially at p. 467-468, "Adsorption Isotherms"; p. 469-470). Amiral et al. also exemplify adsorption of proteins onto microparticles at pH values of 4-10. As such, one would have a *reasonable expectation of success* in optimizing the pH of the coating reaction in the method of Kakabakos et al. as Vaynberg et al. teach that pH variations hardly affect adsorption levels on polystyrene. One would also have a reasonable expectation of success in light of the teachings of Vaynberg et al., Amiral et al., and Lou et al., which all teach adsorption of protein onto polystyrene at pH values up to and/or in excess of pH 10.

With respect to dependent claims 16-17 and 20, Kakabakos et al. teaches incubation times of 1-2 days (24-48 hours). The reference fails to specifically teach incubation times of 4-7, or about 4-7, days as in claims 16 and 20. The reference also fails to specifically teach a buffer having a salt content of about 0.3 to about 1.5 M as in claim 17.

In the instant case, the prior art recognized incubation time as a result-effective variable in the adsorption of proteins onto microparticles, including polystytrene microparticles. For example, Amiral et al. (discussed above) teach that the duration of the reaction is one experimental condition that can be adjusted in order to ensure the stability, reactivity, and preservation of the product (column 9, lines 5-50). This is also taught in Kakabakos et al., in that the immobilization of IgG onto the polystyrene beads increased as a function of time (see Figure 2 and the paragraph bridging pages 493-494).

Absent a showing that the particular claimed range of 4-7 days is critical, it would have been obvious to one of ordinary skill in the art to optimize the length of the incubation out of the normal desire of artisans to improve upon what is already known. In particular, it would have been obvious to increase the incubation time in order to achieve increased adsorption of protein onto the beads, given that increasing incubation time was known to have the effect of increasing the amount of protein immobilized. See MPEP § 716.02 - § 716.02(g) for a discussion of criticality and unexpected results.

With respect to claim 17, ionic strength is also recognized in the prior art as a result-effective variable in the process of protein adsorption to solid surfaces, including polystyrene particles.

For example, Amiral et al. teaches that ionic strength is one experimental condition that is adjusted according to the nature of the product to be assayed when adsorbing proteins onto latex particles, in order to ensure the stability, reactivity, and preservation of the product. In particular, the reference teaches that increasing the ionic strength stabilizes adsorbed immunological reagents (column 9, lines 30-50). The reference exemplifies buffers of ionic strength 0.01-0.5M, which overlaps the claimed range of 0.3-1.5M (column 10, lines 4-21).

Absent a showing that the particular claimed range of 0.3 to 1.5M is critical, it would have been obvious to one of ordinary skill in the art to optimize the ionic strength out of the normal desire of artisans to improve upon what is already known, given that it was known in the prior art to conduct adsorption reactions at ionic strengths overlapping the claimed ranges.

In particular, it would have been obvious to increase the ionic strength in order to increase the stability of the adsorbed protein, as taught by Amiral et al.

24. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kakabakos et al. (in light of Song) in view of Vaynberg et al., Amiral et al., and Lou et al. as applied to claim 17 above, and further in view of Bangs and Gudiband et al.

Kakabakos et al., Vaynberg et al., Amiral et al. and Lou et al. are as discussed above. Kakabakos et al. teaches polystyrene microparticles, but fails to specifically teach that the particles have a size of about 2.8 microns and consist essentially of about 88% polystyrene and 12% magnetite.

Bangs et al. teach superparamagnetic particles, which can be used in radioimmunoassay, ELISA's, and other assays in order to help pull things out of solution more quickly (page 1876). In particular, magnetic particles allow for fast and easy separation of solid and liquid phases.

Gudiband et al. teach the superparamagnetic DYNAL M-280 Dynabeads, which have a 2.8 micron diameter (column 21, Example VII). These are the same beads disclosed in the instant application as consisting of 88% polystyrene and 12% magnetite [0022] such that they necessarily meet the recited limitations as to the composition. Thus, superparamagnetic particles of the recited size and composition were known in the prior art.

Therefore, it would have been obvious to conduct the method of Kakabakos et al. and Amiral et al. using the M280 microparticles taught by Gudiband et al., rather than the polystyrene beads taught by Kakabakos et al. One would be motivated to use the microparticles of Gudiband et al. because they are superparamagnetic, which permits fast and easy separation of the solid and liquid phase in radioimmunoassays (as taught by Bangs); which is the intended use of the coated particles of Kakabakos et al. (see the title).

It would have been obvious to select the known M280 particles based on its art-recognized suitability for its intended use, in that Gudiband et al. teaches that the particles are superparamagnetic. See MPEP 2144.07. One would have a reasonable expectation of success because Gudiband et al. teach that the particles are capable of being coated with protein for use in specific binding assays.

25. Claims 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmid (DE 199 24 643 A1, Applicant's Information Disclosure statement of 5/6/04) in view of Vaynberg et al., Amiral et al., and Lou et al.

Although a translation of the Schmid reference (which is in German) was not submitted by Applicant, this rejection is being made pursuant to a consultation between the examiner and STIC translator J.M. Koytcheff on 11/13/2006.

Schmid teaches methods of coating microparticles with proteins by adsorption (column 1, lines 25-68). Specifically, Schmid teaches a method where microparticles are contacted with a protein in suspension, subjected to uniform heating for 10-90 minutes, maintained at the elevated temperature for 0-50 hours, and then irradiated with UV light (see the entire document, especially column 1, lines 1-11; column 3, lines 1-21; column 4, lines 5-43; the Example, and claim 1). The reference teaches that this process results in microparticles with high binding capacity and reduced bleeding, and allows for large-scale production. Suitable particles include DYNABEADS of size 2.8 microns and having 88% polystyrene and 12% magnetite (column 2, lines 29-35). The proteins to be coated are preferably hydrophobic, and have a size that can vary from 20-300 nm; a preferred size is 50-200 nm since a size ratio between particles and protein is

preferably from >10:1 with >20:1 being particularly preferred (column 2, lines 36-68). The reference teaches that polymerized proteins strengthen the absorption and have a larger number of binding sites. Polymerized streptavidin (poly-SA) is specifically mentioned as having high binding capacity and low bleeding tendency (column 2, lines 59-68). The process allows for protein-charged microparticles useful as a test phase in medicinal, immunological, and diagnostic assays.

The reference differs from the claimed invention in that it fails to specifically teach that the coating pH is selected from a range of about 10.5 to about 12.5. In Schmid, a pH of 7.0 is exemplified (the example). With respect to the length of incubation, the reference also fails to specifically teach the claimed range of 1-10 days, but teaches a total incubation time of 10-90 minutes plus an additional 0-50 hours as noted above.

With respect to the limitation that the combination is incubated for 1-10 days, Schmid teaches that the microparticles and protein are subjected to uniform heating for 10-90 minutes and then maintained at the elevated temperature for 0-50 hours (column 2, lines 1-10, column 3, lines 1-21). Because the claimed ranges overlap the prior art range of 10-90 minutes plus an additional 0-50 hours disclosed by Schmid, a prima facie case of obviousness exists. MPEP 2144.05. As such, and in the absence of evidence of criticality, it would have been obvious to conduct the method of Schmid at the recited incubation times given that the claimed ranges overlap those disclosed in the reference.

With respect to the limitation that the incubation step (step (d) in claim 15) occurs in the absence of covalent coupling, it is acknowledged that Schmid teaches UV light irradiation, which may have the effect of inducing covalent bond formation as argued by Applicant (see

Applicant's Reply of 6/26/07 at pages 15-16). However, as noted above, the reference teaches that this step is performed *after* the combination is incubated or maintained at the elevated temperature. The incubation step therefore would be considered to occur in the absence of covalent coupling since the reference specifically teaches *adsorption* (i.e., non-covalent coating) of the proteins, with UV light irradiation is employed only later. Because the claimed methods employ open transitional language ("comprising"), they do not exclude the use of a later UV light irradiation (or covalent coupling) as an additional step as in the reference.

With respect to the reaction pH, it is known in the art that pH is a result-effective variable in the adsorption of proteins are coated onto particles, as taught by Vaynberg et al., Amiral et al., and Lou et al. It was also known in the prior art to coat proteins onto polystyrene particles at pH values that overlap or lie within the claimed pH range of "about 10.5 to about 12.5".

For example, Amiral et al. also teach that when adsorbing proteins onto latex particles (including polystyrene latex), experimental conditions including pH are adjusted according to the nature of the product to be assaying in order to ensure stability, maximum reactivity, reproducibility, and preservation (see especially column 9, lines 30-50; and column 7, lines 1-11 and 49-66). The reference notes in particular that increasing the pH results in *stabilization* of immunological reagents to be coated, and teaches adsorption at pH in the range of 4-10 (column 9, lines 50-61).

Vaynberg et al. teach that the properties of proteins adsorbed onto polystyrene microparticles can vary in response to pH (p. 467, left column, the second paragraph; p. 470-471, "Adosrption Isotherms"). In particular, increasing pH was found to be associated with a swelling of the hydrodynamic layer thickness, reflecting underlying changes in the structure of the

adsorbed protein layer (Figure 8, p. 470, right column, and p. 471, left column, the first full paragraph). Vaynberg et al. exemplify coating protein onto polystyrene microparticles at high pH values including pH 10 (see p. 469, left column; and Figures 2, 6, and 8 in particular; experiments were conducted over the range pH 5.7-10). The reference also teaches that measurements of the layer thickness and layer hydrodynamic radius (which were found to change as a function of pH) can be used to validate models of the adsorbed protein layer structure (page 472).

Lou et al. also teach that adsorption of proteins onto polystyrene particles is affected by pH, temperature, and other factors (column 4, lines 19-33). In particular, the reference teaches that pH can affect the stability of adsorbed proteins, and report that by adsorbing the protein streptolysin-O at high pH values of 8.5-11.9, the resulting product was more stable and the adsorbed protein substantially retained pre-adsorption characteristics (column 3, lines 34-38; column 4, lines 19-63; column 8, lines 53-59).

Therefore, it would have been obvious to one of ordinary skill in the art to conduct the method of Schmid within the recited pH range of 10.5-12.5 in the course of routine optimization, out of the normal desire of artisans to improve upon what is already known. In particular, it would have been obvious to optimize the pH and in particular to select pH values within the recited pH ranges, given that it was known in the art to coat proteins onto polystyrene microparticles at pH values up to and in excess of pH 10, as taught variously by Vaynberg et al, Amiral et al., and Lou et al. As such, it would have been obvious to optimize within the ranges taught in the prior art, which overlap the currently claimed ranges. In the case where the claimed

ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. MPEP 2144.05.

It would have been obvious to do this since pH is recognized in the prior art as a result-effective variable in methods of adsorbing protein onto polystyrene particles, in that the pH of the coating reaction can affect the structure, stability, reactivity, reproducibility, and preservation, as taught by Amiral et al. Vaynberg et al., and Lou et al.

The Amiral et al. reference provides additional motivation for adsorbing at higher pH, teaching that increasing pH results in stabilization of the coated reagent. Lou et al. also teach that the stability of streptolysin-O protein-coated particles is increased at high alkaline pH (see especially column 4, lines 34-37). As such, it would have been obvious to conduct the method of Schmid at higher pH in order to increase the stability of the coated protein.

Vaynberg et al. teach that the structure of the adsorbed protein can change as a function of pH, and that measurements of the adsorbed protein layer can be used to generate structural models (see especially pages 470-471, "Adsorption Isotherms"; and p. 472). As such, it would have been obvious to increase the adsorption pH in order to generate structural models to study the structure of the protein as a function of pH.

Moreover, Vaynberg et al. teaches that adsorption of protein onto polystyrene is dominated by hydrophobic interactions, such that there is "little variation" in the level of adsorption over a broad range of pH values, including alkaline pH values of up to pH 10 (see the entire document, especially at p. 467-468, "Adsorption Isotherms"; p. 469-470). Amiral et al. also exemplify adsorption of proteins onto microparticles at pH values of 4-10. As such, one would have a *reasonable expectation of success* in optimizing the pH of the coating reaction in

the method of Schmid as Vaynberg et al. teach that pH variations hardly affect adsorption levels on polystyrene. One would also have a reasonable expectation of success in light of the teachings of Vaynberg et al., Amiral et al., and Lou et al., which all teach adsorption of protein onto polystyrene at pH values up to and/or in excess of pH 10.

With respect to claims 16 and 20, Schmid teaches that this time is important for the effectiveness of the method (column 4, lines 5-25). Although Schmid et al. do not specifically teach a length of incubation that is 4-7 days as recited, the reference clearly teaches that incubation time is a result-effective variable impacting the effectiveness of the coating method. Amiral et al. also teach that the reaction time is an experimental condition that may be adjusted according to the nature of the product to be assayed in order to ensure stability, reactivity, and preservation (column 9, lines 30-45).

Therefore, in light of the fact that incubation time was known in the prior art to have effects on protein adsorption, and in the absence of evidence of criticality, it would have been obvious to one of ordinary skill in the art to optimize the incubation time out of the normal desire of artisans to improve upon what is already known.

With respect to claim 17, Schmid teaches 50 mM K2HPO4 (the example). Ionic strength is recognized in the prior art as a result-effective variable in the adsorption reaction of proteins to polystyrene. For example, Amiral et al. teaches that increasing the ionic strength stabilizes adsorbed immunological reagents (column 9, lines 30-50). The reference exemplifies buffers of ionic strength in the range of 0.01-0.5M, which overlaps the claimed range of 0.3-1.5M (column 10, lines 4-21).

See also Lou et al., which also teaches that adsorption of proteins onto polystyrene particles is affected by ionic strength (column 4, lines 19-33).

Given that ionic strength is recognized in the prior art as a result-effective variable in the adsorption of proteins onto polystyrene, it would have been obvious to one of ordinary skill in the art to perform the method at the recited buffer concentration through routine optimization out of the normal desire of artisans to improve upon what is already known. In addition, in light of the teachings of Lou et al. and Amiral et al. that increased ionic strength increases the stability of the adsorbed protein, it would have been obvious to increase the buffer concentration over that exemplified by Schmid.

Response to Arguments

26. Applicant's arguments filed 6/26/07 have been fully considered.

27. With respect to the rejections of claims 1-3, 5, 9, 11-13 and 15-20 under 35 USC 112, 1st paragraph as containing new matter regarding the insertion of the term "about" in relation to the disclosed pH range(s), it is initially noted that Applicant agrees that the currently claimed range of "**about** 10.5 to **about** 12.5" (emphasis added) is broader than the disclosed range of "10.5 to 12.5" (Reply, page 7, third paragraph).

Nonetheless, Applicant argues that the broadening amendments do not represent new matter on the grounds that (1) the disclosed pH values <u>inherently</u> include a certain degree of experimental error and (2) the disclosed pH values <u>implicitly</u> provide support to a person of ordinary skill in the art (Reply, pages 8-9). In both cases, Applicant refers to experimental error in support of the broadening amendments.

This is not found persuasive because neither inherent nor implicit support is seen for the currently claimed broadening amendments. Although the Examiner does not dispute that measurement of pH values might be associated with experimental error, this does not provide support for the broadening amendments now claimed because the instant specification does not mention experimental error or otherwise indicate that the disclosed ranges are intended to be approximate.

As such, Applicant has not established that the broadening amendments are inherently or implicitly supported (as per the Decision Tree in the Written Description Guidelines to which Applicant points), because the skilled artisan, in reading the specification, might understand that the disclosed ranges are meant to be precise and/or have already taken into account experimental error.

Applicant also refers to *BJ Services Co. v. Halliburton Energy Services Inc.*; however, the facts of that case differ because they did not involve new matter or the written description requirement.

Applicant further argues that pH 13.5 cannot be considered to be "about" 12.5 due to the logarithmic nature of the pH scale (Reply, page 7). The Examiner's selection of the example of pH 13.5 was made simply to illustrate how pH values outside of the disclosed range are now encompassed by the broadening amendments (see the previous Office action at page 10).

As best understood, Applicant argues in essence that the scope of the claims has been broadened, but not as much as the Examiner suggests. Such the arguments are viewed as tangential to the instant question of whether one skilled in the art would have envisaged possession of the currently claimed invention. The amendments do clearly change the scope of

the claims. It is unclear how a determination as to how much they have been broadened, i.e. what exact values would fall within the claim scope, would be relevant to the instant rejection under 112, 1st paragraph.

Furthermore, given that the specification does not specifically define or otherwise indicate what values would be considered "about" pH 10.5-12.5, Applicant's arguments that the insertion of this term only broadens the scope of the claim to a certain degree that is reflective of experimental error are unsupported by the evidence of record. The Examiner acknowledges the logarithmic nature of the pH scale, but the specification does not define the term "about" or indicate that the term is to be interpreted in the manner Applicant is currently arguing.

The specification exemplifies pH 9-13 (Figure 1) and does not provide any evidence of criticality for pH 10 vs. pH 10.5. As such, there is no evidence of record to indicate that the skilled artisan would interpret the currently claimed range of "about" pH 10.5 to "about" pH 12.5 to only encompass differences of, e.g., less than 0.4 pH units (see Applicant's Reply at pH 14, in which it is argued that pH 9.6 is not "about" pH 10).

Therefore, it is maintained that the specification fails to convey evidence of possession of the currently claimed subject matter.

28. Applicant's arguments with respect to the rejections of claims 13 and 17 as containing new matter are not persuasive for similar reasons (Reply, the paragraph bridging pages 9-10). As above, Applicant does not dispute that the currently claimed methods involving a salt content of "about" 0.3 to "about" 1.5M represent broadening amendments (Reply, page 10, the first paragraph).

Applicant argues that the term "about" is being used in a manner consistent with common usage, which does not appear to be relevant to the instant rejection under 112, 1st paragraph. Applicant refers again to *BJ Services Co. v. Halliburton Energy Services Inc;* however, the facts of that case involved considerations of the term "about" in relation to enablement and definiteness and not to written description or new matter issues.

Applicant again points to experimental error and argues that one of ordinary skill in the art recognizes that any stated measurement value would inherently include some level of error (Reply, page 10). However, it does not necessarily follow that one skilled in the art would understand the disclosed ranges to be read as approximate in the manner now claimed. Rather, one skilled in the art might conclude that the values were precise, or that the inventors had already taken into account experimental error when presenting the disclosed ranges. Because there is nothing in the specification to convey that the disclosed values are meant to be approximate, one skilled in the art cannot envisage possession of the currently claimed invention. Furthermore, in the absence of a specific definition of the term "about" in the specification, the claimed range cannot be construed as just encompassing experimental error.

29. Similarly, Applicant argues with respect to the rejections of claims 9 and 18 that the insertion of the term "about" in relation to the disclosed composition of the microparticles does not represent new matter because those skilled in the art would understand the recitation of 88% polystyrene and 12% magnetite to include some variance in those listed percentages due to practical manufacturing techniques and experimental error associated with such measurements (Reply, pages 10-12).

This is not found persuasive reasons similar to those discussed above. There is nothing in the specification to indicate that the disclosed percentages are meant to be read as anything other than precise. Furthermore, the broadening amendments cannot be construed as being limited only within some range of experimental error, since there is nothing in the specification defining "about" in this context.

In addition, Applicant has not submitted any evidence of record to establish that manufacturing of the disclosed DYNABEADS is necessarily and always imprecise as asserted.

As stated in the above rejection, the specification only mentions the values 88% and 12 % in the context of:

Applicant further argues (Reply, page 12) that the clear intent was not to be limited to these two specific microparticles (M-280 and M-270), pointing to the "for example" language in the following passage from the specification at [0022], which reads:

> DYNABEADS from the DYNAL Company having a size of ca 2.8 μm and consisting of 88% polystyrene and 12% magnetite such as the hydrophobic beads M-280 or the epoxy beads M-270 are, for example, suitable.

This is not found persuasive because although it is clear from the above passage that other particles may be suitable, there is no direction to select other particles that have the same size and approximate composition as DYNABEADS. The only reference made to particles consisting of 88% polystyrene and 12% magnetite (or "about" thereof) is in describing properties of the M-270 and M-280 DYNABEADS from the DYNAL Company. The specification does not direct the skilled artisan to select other beads having these characteristics, and therefore fails to convey evidence of possession of the currently claimed subgenus.

Applicant further argues that one of ordinary skill in the art would readily recognize that other beads having the recited properties could be used in the context of the present invention, and that Applicants had possession of such embodiments (Reply, the paragraph bridging pages 12-13). This is not found persuasive because whether a skilled artisan would have found it obvious to select other beads with the currently recited composition, and whether he would then conclude Applicants to have been in possession of such other beads, are two separate questions. Since obviousness is not the standard for the addition of new limitations to the disclosure as filed, it does not necessarily follow that if a skilled artisan could conceive of other embodiments that he would also understand Applicants to be in possession of same. See Lockwood v. American Airlines, Inc., 107 F.3d 1565 (Fed. Cir. 1997) ("A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations.").

The instant claims introduce a new subgenus of microparticles, which may include particles other than DYNABEADS but which have some of the same properties as these beads. This cannot be readily envisaged from the above passage. Although the skilled artisan would envisage that microparticles other than DYNABEADS might be suitable, there is no direction given to select other particles having similar chemical composition as DYNABEADS.

Therefore, given that the specification discloses only DYNABEADS from the DYNAL Company having the precisely stated composition of 88% polystyrene and 12% magnetite, and that no reference is made to other particles of this composition, and further that there is no

indication that the disclosed composition is intended to be approximate, it is maintained that the amendments are not adequately supported by the specification.

30. With respect to the rejection of claim 15 under 35 USC 102(b) as being anticipated by Kakabakos et al., Applicant's arguments (see page 14) have been fully considered but are not persuasive.

Applicant argues initially that the reference teaching of pH 9.6 does not anticipate the previously claimed pH range of about pH 10 to about pH 12.5, due to the logarithmic nature of the pH scale (Reply, page 14). Similarly, Applicant argues that the currently claimed pH range of "about 10.5 to about 12.5" distinguishes the present invention over that of Kakabakos et al., since due to the logarithmic nature of the pH scale, pH 9.6 has a 8X difference in [H+] concentration.

However, the specification does not specifically define the term "about" in the context of the claimed ranges, or otherwise provide a standard for ascertaining what values would be encompassed. Such a standard as Applicant is now arguing is not found in the specification. There is nothing in the specification to indicate that the term "about" must be interpreted as referring only to minor variations attributable to experimental error.

Furthermore, the specification discloses that the claimed methods are performed under "strongly alkaline conditions" [0014], preferably "between pH 10.0 and pH 12.5" [0015], [0030]. When long time intervals are used, "pH ranges of 10.5 to 12.5 and in particular of 11.0 to 12.0 are particularly preferred" [0030]. The pH ranges of pH 9.0-12.5 and 10-12.5 are exemplified ([0016], [0045] and Figure 1.

No experimental evidence of criticality is seen or disclosed in the specification for pH 9.6 (as disclosed in Kakabakos et al.) vs. the claimed range of pH 10.5-12.5. Similarly, no criticality is seen for pH 10 vs. pH 10.5. The experiments in the specification do not support Applicant's arguments that there are substantial differences between pH 9.6 and pH 10, between pH 9.6 and 10.5, between pH 10 and 10.5, etc. such that one skilled in the art would understand the term "about" to permit only small variations.

Therefore, given the broadest reasonable interpretation, it is maintained that pH 9.6 would be encompassed by the claimed range.

31. With respect to the rejections of claims 15-20 under 35 USC 103(a) as being unpatentable over Schmid in view of Vaynberg, Amiral et al., and Lou et al., Applicant's arguments (see pages 15-21) have been fully considered but are not persuasive of error.

Applicant initially argues that a copy of the translation of the Schmid reference that the Examiner relied upon was not provided to Applicant's (Reply, page 15). It appears that Applicant has misunderstood. As stated in the body of the rejection and as clarified in the Interview Summary of 3/5/07, the Office has not obtained a written translation of the Schmid reference. Rather, the rejection was based on an oral consultation with a STIC translator, the results of which were made of record in the body of the rejection. This is in accordance with MPEP 901.05(d). The Examiner chose oral consultation with a translator appropriate in this case (vs. the expense of obtaining a full written translation) because Applicants had cited the reference on an IDS and also because it was presumed that Applicants, as German citizens, would be able to understand the reference. Should the Office obtain a written translation of the reference in the future, a copy will of course be shared with Applicant and made of record.

Applicant further argues that Schmid teaches away from the use of long incubation times, since it teaches a preference for incubation time of less than 20 hours (Reply, page 15). This is not found persuasive because a statement of alternatives or preferred embodiments does not rise to the level of a "teaching away". A reference "teaches away" if a person of ordinary skill in the art would have been discouraged or led to a divergent path from the one taken by the inventors. In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994)("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.").

Here, rather than discourage or disparage, Schmid simply that up to 20 hours is preferable, but that coating may be performed for 0-50 hours. See In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004)("[M]ere disclosure of alternative designs does not teach away."). Statement of a preference does not constitute a teaching away from all other disclosed embodiments.

32. Applicant further argues that the Schmid reference does not meet the claim limitation of occurring "in the absence of covalent coupling" as currently recited in step (d) of claim 15 (Reply, the paragraph bridging pages 15-16). In particular, Applicant argues that Schmid teaches UV irradiation, which would necessarily result in covalent bond formation.

Applicant's arguments that the UV irradiation step performed in Schmid would necessarily involve covalent bond formation are compelling, in that it would seem that UV light would have the effect of cross-linking of the adsorbed proteins to each other. However, in Schmid the UV irradiation step is performed after the protein-microparticle is incubated for 0-50

hours, i.e. as a separate step. In other words, it is performed after step (d) of claim 15. Because of the open transitional language employed by Applicant ("comprising"), additional steps that involve covalent coupling are not excluded by the method, so long as the claimed incubation step (d) is performed in the absence of covalent coupling. Therefore, the teaching reads on the claim limitation since UV irradiation was not performed until after the combination was incubated for 0-50 hours at the maintained high temperature.

33. Applicant further argues (Reply, page 16) that none of the references alone or together suggest that a pH range as high as 10.5-12.5 should be used to adsorb proteins to microparticles, to which the Examiner disagrees for reasons of record. To the contrary, it was known to adsorb proteins to microparticles at ranges overlapping the claimed range, as taught in Lou (see above and the previous Office action at page 20). Even without such an explicit teaching, however, it is maintained that evidence of criticality of the currently claimed range is necessary to establish non-obviousness, given that it was known in the art to optimize pH.

34. Applicant further argues (Reply, page 16) that Amiral teaches away from increasing the pH since it teaches that this may have negative effects as well. However, as noted above, a mere statement of alternatives does not rise to the level of a teaching away. Rather than discourage or disparage increasing the pH, Amiral teaches that (as with many courses of action) there are known benefits but also known disadvantages to doing this.

35. Applicant further argues (Reply, page 17) that the Amiral and Vaynberg references fail to teach the pH range recited, which is not found persuasive since it amounts to a piecemeal analysis of the references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the

rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

36. In response to applicant's argument that Vaynberg focuses on maximizing loading but does not discuss stability or reduced bleeding (Reply, page 17), the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Furthermore, it is noted that Amiral et al. teach that increasing pH may have the effect of improved stability (column 9).

37. Applicant's arguments with respect to the particulars of the Vaynberg reference as they are alleged to "teach away" from the claimed invention (Reply, pages 17-18) have been previously advanced in substantially similar form and are not persuasive for reasons of record. See, e.g. the Office action mailed 11/28/06 at pages 32-35 and the Office action mailed 4/11/06 at pages 16-18. The arguments are not persuasive to establish non-obviousness for reasons of record.

Furthermore, the instantly applied combination of references when taken together establish that pH was recognized as a result-effective variable in the adsorption of proteins onto polystyrene particles, and that it was known to adsorb at high pH, including at values that overlap the claimed range. In light of these facts, the rejection is maintained as proper in the absence of evidence of criticality for the currently claimed range.

38. In response to applicant's argument that Lou et al. teaches use of carbodiimide, which teaches away from methods in the absence of covalent coupling (Reply, pages 19-20), the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into

the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Furthermore, such arguments constitute a piecemeal analysis of the references. In the instant case, the Schmid reference has been relied upon for its teaching of the claimed incubation step, which occurs prior to (and thus in the absence of) cross-linking by UV irradiation. The Lou reference has been relied upon to teach that pH, temperature, and other factors are known to be result-effective variables in protein adsorption onto microparticles.

39. Similarly, Applicant's arguments that Lou et al. fail to teach or suggest the long incubation times claimed (Reply, page 19) are not persuasive because they amount to a piecemeal analysis of the references.

40. Applicant further argues (Reply, pages 20-21) that optimization of a procedure can only occur when there is guidance as to what parameters should be varied to produce the optimal result. This is not found persuasive because such in the instant case, the prior art does teach what parameters to vary. As detailed in the rejection, the prior art recognized that pH, temperature, time and other factors are result-effective variables in the non-covalent adsorption of proteins onto microparticles. Thus, the argument that the prior art does not provide an indication of which parameters to optimize is not persuasive because it does not reflect the facts of the instant case.

Given that such result-effective variables were recognized in the prior art, it is maintained that a person of ordinary skill would have good reason to pursue such known options. Absent evidence of unexpected results, such routine optimization is determined to involve no more than

ordinary skill and common sense. See *KSR International Co. v. Teleflex Inc.,* 550 U.S.--, 82 USPQ2d 1385 (2007).

41. Applicant further argues (Reply, page 16, first paragraph) that Applicants have directly compared the results obtained by the method of Schmid with the presently claimed method and have found superior results. In particular, Applicant argues that the unique combination of selected conditions has produced a surprisingly improved composition, specifically in terms of a homogeneous distribution with lower proportion of dimeric, trimeric, and higher aggregates compared to those obtained by the prior art methods as indicated in Figure 2 vs. Figures 3-4 (Reply, page 21). Unexpected results in terms of low bleeding rates are also alleged.

The evidence of secondary considerations have been considered but are not found persuasive to establish non-obviousness because the evidence is not commensurate with the scope of the claims. No evidence that directly compares the method of Schmid with <u>the presently claimed method</u> has been advanced. Applicant argues that the data in Figures 3 and 4 show vast improvement over that of Figure 2 (prior art method). However, the experiments used to create the data of Figures 3-4 do not represent a depiction of the claimed invention. The specification discloses at [0018]-[0019] that the data of Figures 3-4 were collected on DYNAL M-280 beads coated as in Example 1, which discloses coating DYNAL beads at a pH range of <u>10.0-12.5</u> [0045]. However, the claims recite the pH range of <u>10.5-12.5</u>. Given that Applicant has argued, in effect, that pH 9.6 is substantially dissimilar from pH 10 due to the logarithmic nature of the pH scale (Reply, page 14), such data cannot be reasonably extrapolated to the currently claimed pH range, which differs by a larger amount than that of pH 9.6 vs. pH 10.0. Applicant has

provided no evidence of criticality to support a fundamental difference between pH 9.6 and pH 10, or especially between pH 10 and 10.5.

Therefore, the evidence of non-obviousness fails to outweigh the evidence of obviousness because Applicant has not established evidence of criticality for the currently claimed pH range.

42. With respect to the rejections of claims 16-17 and 20 under 35 USC 103(a) as being unpatentable over Kakabakos et al. (in light of Song) in view of Amiral et al., Applicant's arguments (Reply, pages 21-22) have been fully considered but are not persuasive.

Applicant argues that the claims require a minimum of pH 10.5 (Reply, page 21), to which the Examiner disagrees because of the use of the broad terminology "<u>about</u>" in relation to the claimed range. Furthermore, Applicant has not provided evidence of criticality of the currently claimed pH range that would rebut the presumption of obviousness.

Applicant further argues that the general statement of Amiral that the pH, ionic strength, volume, temperature, time and concentration of ligand can be optimized fails to provide sufficient guidance but merely represents an "invitation to experiment" (Reply, the paragraph bridging pages 21-22). This is not found persuasive because given such a finite number of parameters to optimize, it would have been obvious to try to optimize by choosing among such known result-effective parameters, for example in order to ensure desired qualities like stability, reactivity, etc. of the final product. Absent evidence of criticality, it is maintained that the evidence of non-obviousness fails to outweigh the evidence of obviousness.

Applicant further disputes the Examiner's contention that Kakabakos et al. teaches that immobilization increased as a function of time, arguing that the passages indicated by the Examiner refer to the effect of temperature (Reply, page 22, first full paragraph). However,

Applicant's statements that immediately follow take note of the fact that most of the immobilization "occurs in less than 5 hours", correctly reflecting that time is also a variable in the experiment of Figure 2. Indeed, it can be clearly seen in Figure 2 that the amount of bound IgG increases (as indicated by the Y-axis) with increasing time (on the X-axis).

Applicant further argues that in Kakabakos et al. most of the immobilization occurs in less than 5 hours and questions whether the slight increase shown post 20 hours is statistically significant (Reply, page 22). Such opinions as to the teachings of the reference are seen as tangential to the issue at hand, given that Applicant has not demonstrated evidence of criticality, in this case for 20 hours vs. 24 hours. Furthermore, such speculations do not have the probative value of objective evidence. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

Applicant does not separately argue the limitations of dependent claims 16-17 and 20 (Reply, pages 22-23).

Conclusion

43. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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